

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

Brief Description of the Claimed Invention

The presently claimed invention is directed a delivery system for a supplement which comprises: (i) one or more supplements selected from a particular list; and (ii) a biocompatible tissue sealant composition. When used, the biocompatible tissue sealant composition forms a fibrin matrix, which contains the supplement(s). The supplement is subsequently released from this fibrin matrix into the environment of use.

The biocompatible tissue sealant composition of the claimed delivery system comprises fibrinogen, or a derivative or metabolite thereof, in an amount that forms a fibrin matrix in the presence of thrombin, Factor XIII, and Ca^{++} (or other materials known by those skilled in the art to induce fibrin formation). The biocompatible tissue sealant composition may optionally also comprise one or more of thrombin, Factor XIII and Ca^{++} in addition to fibrinogen, but one or more of these components necessary for the formation of the fibrin matrix from fibrinogen may be provided in various embodiments of the claimed invention by endogenous body fluids or cells of the host.

The fibrin matrix formed by the biocompatible tissue sealant composition upon activation of its fibrinogen component by suitable agents has many of the characteristics of an ideal biodegradable carrier. For example, it can be formulated to contain only proteins of the host, such as human proteins, thus eliminating or minimizing immunogenicity problems and foreign-body reactions. Because the biocompatible tissue sealant composition requires activation of the fibrinogen component to form the fibrin matrix from which the supplement is released, administration of the claimed delivery system is highly controllable. Moreover, because a fibrin matrix adheres to the cells or tissues of the host, it is maintained at the site of

administration, thereby ensuring sustained delivery of the supplement at the desired site.

Finally, the claimed delivery system does not need to be removed from a host's tissue after use because the fibrin matrix is degraded by the host's fibrinolytic system.

The supplement component of the claimed delivery system may be any one of a number of active agents for which delivery to or into a host's tissue(s) is desired. Another particular advantage of the claimed invention is that it allows sustained release of a supplement or supplements to a localized area, which tends to facilitate the action of the claimed supplements. For example, it has been shown that some growth factor receptors must be occupied for twelve (12) hours to produce a maximal biological effect. By employing the claimed delivery system, prolonged contact between a growth factor (or factors) and the appropriate receptor(s) can be maintained, thereby ensuring maximum effect.

Objection to the Specification/Rejections under 35 U.S.C. § 112

In the outstanding Office Action, the Examiner has objected to the specification as failing to describe the invention in such terms as to allow one skilled in the art to make and/or use the invention. The Examiner has rejected claims 12-20 on the same grounds. Applicants respectfully traverse this objection and rejection.

The presently claimed invention is briefly described above. Contrary to the Examiner's assertion, the specification of the above-identified application does teach one skilled in the art how to make and use this invention. While, as noted by the Examiner, it may be that some experimentation may be required to practice the claimed invention, that experimentation is not undue and therefore does not render the present specification non-enabling. Withdrawal of the outstanding objection and rejection are therefore requested.

The factors to be considered in determining whether a disclosure would require undue experimentation include: (i) the quantity of experimentation necessary; (ii) the amount of guidance provided; (iii) the presence of working examples; (iv) the nature of the invention; (v) the state of the art; (vi) the relative skill of those in the art; (vii) the predictability of the art; and (viii) the breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1408 (Fed. Cir. 1988). In light of these factors, as discussed in more detail below, the present specification is enabling for the full scope of the pending claims without undue experimentation.

As noted in the section above, the present invention relates to a delivery system for a supplement (or supplements). This delivery system is based on a fibrin matrix, formed by activation of fibrinogen (or derivative or metabolite thereof) in the biocompatible tissue sealant component, the resulting fibrin matrix containing one or more supplements for delivery. The presently claimed invention is premised, in part, on the discovery that a supplement(s) contained in such a fibrin matrix can be delivered to a predetermined area, such as the tissue of a patient, by release from this fibrin matrix when it is placed in the environment of use.

The present specification provides ample guidance to one skilled in the art to make and use the fibrin matrix employed in the inventive delivery system. For example, the present specification discloses the basic components of the biocompatible tissue sealant that forms the fibrin matrix (*see, e.g.*, page 37, line 23, to page 38, line 4). The present specification discloses how to incorporate a supplement into the biocompatible tissue sealant (*see, e.g.*, page 37, lines 5-15 and the Examples).

In addition, a number of examples are provided in the specification that show the inclusion in a biocompatible tissue sealant of various supplements from among the groups

recited in the claims. These examples also show the delivery of the supplements from the fibrin matrix into the environment of use (*see, e.g.*, page 62, Example 4; page 69-70, Example 9; page 71-72, Example 10; page 83-91, Example 13; page 91-97, Example 14; page 98-99, Example 17, page 102-105, Example 19; page 117-118, Example 23; and page 118-119, Example 24).

Given this level of disclosure, the amount of experimentation required to practice the presently claimed invention is not excessive. Rather, the skilled worker need only select a given supplement (or supplements) for which delivery to a patient is desired and incorporate that into the biocompatible tissue sealant as described in the specification. The resulting composition can then be assayed, for example according to any one of the methods disclosed in the present specification, for its efficacy as a delivery system for the supplement.

Finally, it should be noted that if a particular supplement/tissue sealant composition does not exhibit the requisite release of the supplement into the environment of use, then such a composition would not be a "delivery system" (and therefore would be outside the scope of the present claims).

Thus, considering the *Wands* factors noted above, no undue experimentation would be required to practice the presently claimed invention. Withdrawal of the outstanding objection and rejection are therefore requested.

As a final matter, applicants respectfully submit that the Examiner's comments in the Office Action regarding "certain problems" associated with the field of therapeutic antibodies are not well taken in the context of the present application and the amended claims above. Clarification is therefore requested.

For example, applicants agree that, "for the particular condition, wound, disease or cancer, appropriate antibodies must be selected that are problem-specific." Suitable antibodies for particular uses, such as various wounds, diseases and cancers, however, were known and available to workers skilled in the art at the time the present invention was made. The Examiner's attention is directed, for example, to *Remington's Pharmaceutical Sciences*, 18th ed., A. Gennaro, ed., Mack Publishing Company, Easton, Pennsylvania (1990), pp. 807-9; 1141; 1161-62; 1379-1404; 1425; 1427-28.

Similarly, the discussion concerning various modes of administration is not seen to be relevant to the claimed invention. More specifically, when used, the presently claimed delivery system is applied to the surface where the supplement is to be delivered, such as an internal or external wound. Hence, any discussion of i.v. administration does not appear particularly germane to the presently claimed invention.

With respect to other forms of administration, as discussed above, the present application fully enables one skilled in the art to prepare the claimed delivery system containing one or more supplements, such as antibodies, and apply the delivery system to the environment of use. As further discussed above, the present application contains a number of examples showing the inclusion of various supplements, including proteins, in fibrin matrices and the subsequent delivery of those supplements to the environment of use. The present specification therefore fully enables the skilled worker to make and use the claimed invention.

For all these reasons, withdrawal of the outstanding objection and rejection are respectfully requested.

Conclusion

Applicants note with appreciation that the Examiner considers the presently claimed invention to be new and non-obvious in view of all of the cited documents. In addition, all of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicants believe that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Donald R. McPhail
Attorney for Applicants
Registration No. 35,811

Date: 7/7/97

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005
(202) 371-2600